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plasma cells are dying or ceasing antibody production; this generally signifies that the immunogen has been eradicated. Thus, the duration of a humoral imnume response is limited primarily by the duration of the antigenic stimulus and by the relatively short life spans of the plasma cells involved in the response.

Subsequent encounters with the same immunogen lead to responses that are qualitatively similar to the primary response but manifest marked quantitative differences (see Fig 4-7). In such a secondary, or anamnestic, immune response, the lag period is shortened and antibody levels rise more rapidly to a much higher steady-state level, thereafter remaining in the serum at detectable levels for much longer periods. The large numbers of antigen-specific memory T and B cells generated during the primary response are responsible for the rapid kinetics and the greater intensity and duration of secondary responses.

## PROGRAMMED CELL DEATH IN THE IMMUNE SYSTEM

Antigen-dependent proliferation of a lymphocyte clone is an example of positive selection; that is, the antigen promotes growth of the cells on which it acts. Under some conditions, however, contact with antigens or other stimuli results in negative selection of a responsive clone, meaning that cells in the clone selectively die. Negative selection of lymphocytes is a common event and is essential to the ability of the immune system to discriminate self from nonself. In particular, most virgin T or B cells whose antigen receptors recognize components found in normal host tissues are thought to be selectively killed before they leave the bone marrow or thymus, as a means of protecting the host against attack by these potentially autoreactive (ie, self-reactive) cells. This may account for the observation that at least 99% of developing thymocytes die within the thymus (see Chapter 3). Thus, the clonal composition of the immune system is shaped not only by positive clonal selection but also by the active elimination of potentially deleterious

Lymphocytes frequently die after being instructed to commit suicide by signals in their environment. These signals often include events such as antigen binding to surface immunoglobulins or TCRs which, under other circumstances, would lead to clonal proliferation. When delivered in particular combinations or at certain vulnerable stages in a cell's life, however, these signals instead induce death by apoptosis (see Chapter 1). Because death in these cells is preceded by biochemical changes indistinguishable from those of activation, it is often termed activation-induced cell death (AICD). AICD triggered by contact with self-antigens is an important mechanism for climinating autoreactive B- and T-lymphoid cells (see

Chapters 8 and 9), and occurs commonly among normal thymocytes, bone marrow progenitors, and germinal center B cells.

Another signaling pathway that is especially important for killing of and by lymphocytes involves a surface transmembrane protein called Fas (MW 45.000; also called APO-1 or CD95), which is expressed constitutively by many normal or neoplastic cell types as well as on activated B and T lymphocytes. The extracellular portion of Fas serves as a receptor for a different surface protein-a homorrimer of polypeptides called Fas ligand (FasL), found on many activated T cells and certain other cell types. When cells expressing these two proteins contact one another, binding of FasL causes Fas to trimerize and this, in turn, induces apoptosis in the Fas-bearing cell. The signaling pathway involved is incompletely understood, but depends on an 80-amino-acid "death domain" in the cytoplasmic portion of Fas. Cytotoxic T lymphocytes exploit this as one mechanism for killing: activated Tc cells express FasL, which enables them to induce apoptosis in target cells that express Fas. But lymphocytes themselves can also be killed in this way. For example, after prolonged or repeated activation, helper T cells express both Fas and FasL, and so may kill either themselves or one another; this is thought to be one mechanism for limiting the intensity of an immume response. The same mechanism might also act to eradicate autoreactive T<sub>H</sub> cells that encounter abundant self-antigens in peripheral tissues and indeed, mutations in Fas are responsible for certain rare autoimmune diseases. Fas-mediated killing may also account in part for the phenomenon of immune privilege—the observation that foreign tissues transplanted to certain sites in the body are much less prone to immunologic attack than they would be at other sites. Cells in two of the best studied privileged sites (the testes and anterior chamber of the eye) have been found to express FasL constitutively; this tends to induce apoptosis of any lymphocytes that become activated (and hence express Fas) within these tissues, and so suppresses any local immune responses.

The importance of negative selection is also illustrated by follicular lymphoma, the most common form of B-cell cancer in humans (see Chapters 7 and 46). A major factor in the genesis of this disease is Bcl-2-a normal cellular protein that acts to inhibit apoptosis in some lymphocytes and other cell types (see Chapter 1). Follicular lymphoma arises when a clone of B cells expresses abnormally high levels of Bcl-2 protein and so becomes resistant to killing; as a result, these cells accumulate in abnormally large numbers and eventually evolve into a cancer. This implies that a high, controlled rate of programmed lymphocyte death normally benefits the host by restricting the growth of individual clones and of the lymphoid population as a whole, providing a counterforce against the stimuli that might otherwise drive excessive lymphocyte proliferation.